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PATENT SPECIFICATION

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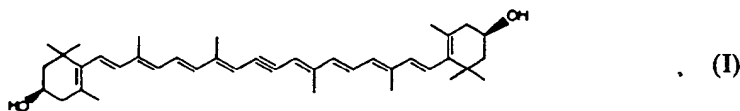
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(54) [3R,3'R]-15,15'-DIDEHYDRO-ZEAXANTHIN

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

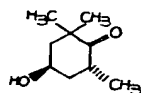
The present invention is concerned with [3R,3'R]-15,15'-didehydro-zeaxanthin of the formula



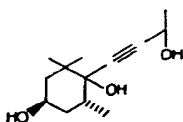
[3R,3'R]-15,15'-Didehydro-zeaxanthin of formula I hereinbefore is of value in that it can be partially hydrogenated to give [3R,3'R]-zeaxanthin, the latter being identical with the natural carotenoid which is present, in particular, in maize. [3R,3'R]-Zeaxanthin is therefore extremely useful for the improving and colouring of foods, cosmetics and pharmaceutical preparations and is especially suitable for the pigmentation of egg yolks and the colouring of fat and skin of poultry.

The substituents in the structural formulae given in this specification are characterised by the notation insofar as they lie in front of the plane of the molecule and by the notation insofar as they lie behind the plane of the molecule. The substituents in the structural formulae which are not stereochemically characterised in any particular manner in this specification can have either the R or S configuration. The compounds can also be present as mixtures of the R- and S-isomers.

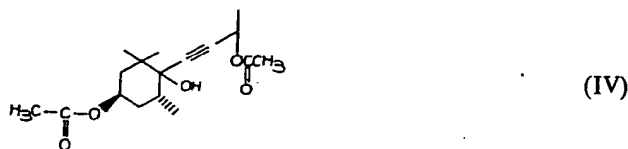
[3R,3'R]-Didehydro-zeaxanthin of formula I hereinbefore can be prepared, for example, by reacting [4R,6R]-4-hydroxy-2,2,6-trimethyl-cyclohexanone of the formula



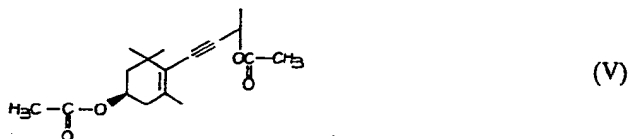
with but-3-yn-2-ol, suitably after the free hydroxy group has been marked by treatment of the ketone with its propenylmethyl ether, acetylating the resulting 2-hydroxy-4-[[4R,6R]-1,4-dihydroxy-2,2,6-trimethyl-cyclohex-1-yl]-but-3-yne of the formula



to give 2-acetoxy-4-[[4R,6R]-4-acetoxy-1-hydroxy-2,2,6-trimethyl-cyclohex-1-yl]but-3-yne of the formula



5 dehydrating the diacetate of formula IV to give 2-acetoxy-4-[[4R]-4-acetoxy-2,2,6-trimethyl-cyclohex-1-en-yl]-but-3-yne of the formula

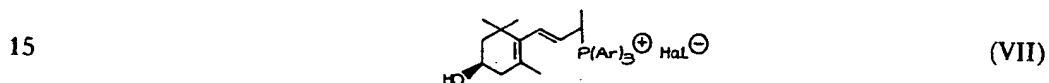


and hydrogenating the acetylenic bond present to an ethylenic bond to give [3R]-3-hydroxy- β -ionol of the formula



10 and then either

(a) converting the [3R]-3-hydroxy- β -ionol of formula VI by reaction with a triarylphosphonium halide or with a triarylphosphine in the presence of a mineral acid into a 4-[[4R]-4-hydroxy-2,2,6-trimethyl-cyclohex-1-en-1-yl]-but-3-ene-2-triarylphosphonium halide of the general formula



wherein Ar represents an aryl group and Hal represents a halogen atom such as a bromine atom, and condensing this Wittig salt of formula VII with 4,9-dimethyldodeca-2,4,8,10-tetraen-6-yne-1,12-dial to give [3R,3'R]-15,15'-didehydrozeaxanthin, or

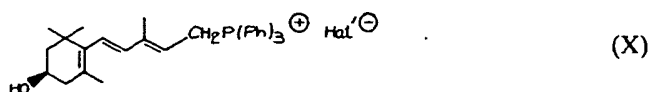
20 (b) converting the [3R]-3-hydroxy- β -ionol of formula VI by oxidation into [3R]-3-hydroxy- β -ionone, reacting said β -ionone with sodium acetylide to give [3R]-3-hydroxyethynyl- β -ionol of the formula



25 catalytically hydrogenating said β -ionol of formula VIII, converting the resulting [3R]-3-hydroxy-vinyl- β -ionol of the formula



by reaction with triphenylphosphonium chloride or bromide or with triphenylphosphine in the presence of a mineral acid into a [3R]-3-hydroxy- β -ionylidenethyl-triarylphosphonium halide of the general formula



wherein Hal' represents a chlorine or bromine atom, and condensing said phosphonium salt of formula X with 2,7-dimethyl-octa-2,6-dien-4-yne-1,8-dial to give [3R,3'R]-15,15'-didehydro-zeaxanthin.

The [4R,6R]-4-hydroxy-2,2,6-trimethyl-cyclohexanone of formula II hereinbefore and a process for its preparation are claimed in the specification of our copending Application for Letters Patent No. 34605/75 (now Serial No. 1,508,195).

The following Examples illustrate the manner in which the [3R,3'R]-15,15'-didehydro-zeaxanthin can be prepared:

Example 1.

9.8 g of [4R,6R]-4-hydroxy-2,2,6-trimethyl-cyclohexanone are dissolved in 6.8 g of isopropenyl methyl ether. The solution is treated in the cold with 4 drops of a 1% methanolic solution of p-toluenesulphonic acid, then neutralised by the addition of triethylamine and subsequently evaporated under reduced pressure. The resulting [4R,4'R]-4,4'-(isopropylidenedioxy)-bis[6R]-2,2,6-trimethylcyclohexanone] melts at 109°—111°C after recrystallisation from hexane.

A solution of ethylmagnesium bromide in tetrahydrofuran (prepared in the usual manner from 18.2 g of magnesium, 81.8 g of ethyl bromide and 200 ml of tetrahydrofuran) is treated dropwise within 30 minutes at room temperature, with 26.6 g of but-3-yn-2-ol in 75 ml of tetrahydrofuran. The mixture is stirred under reflux conditions for 2 hours and subsequently treated dropwise with a solution of 11.1 g of [4R,4'R]-4,4'-(isopropylidenedioxy)-bis[6R]-2,2,6-trimethylcyclohexanone] in 75 ml of tetrahydrofuran. The mixture is stirred for 12 hours under reflux conditions, subsequently acidified by the addition of 1-N sulphuric acid, then saturated with common salt and extracted with ether. The ether extract is washed to neutrality with an aqueous common salt solution, dried over sodium sulphate and evaporated under reduced pressure. The resulting oily 4-[[4R,6R]-1,4-dihydroxy-2,2,6-trimethylcyclohex-1-yl]-but-3-yn-2-ol is subsequently acetylated by treatment with acetic anhydride in the presence of pyridine. There is obtained 2-acetoxy-4-[[4R,6R]-1-hydroxy-4-acetoxy-2,2,6-trimethyl-cyclohex-1-yl]-but-3-yne as an oil, which is purified by adsorption on silica gel using n-hexane/ether (3:2) as the eluant.

8.6 g of 2-acetoxy-4-[[4R,6R]-1-hydroxy-4-acetoxy-2,2,6-trimethyl-cyclohex-1-yl]-but-3-yne are dissolved in a mixture of 53.5 ml of pyridine and 22 ml of phosphorus oxychloride and heated to 100°C for 18 hours. The mixture is then cooled and introduced into ice/water. The mixture is extracted with ether and the ether extract is washed to neutrality with water and 1-N sulphuric acid, dried over sodium sulphate and evaporated under reduced pressure. The resulting oily 2-acetoxy-4-[[4R]-4-acetoxy-2,2,6-trimethyl-cyclohex-1-en-1-yl]-but-3-yne is purified by adsorption on silica gel using hexane/ether (4:1) as the eluant.

4.0 g of 2-acetoxy-4-[[4R]-4-acetoxy-2,2,6-trimethyl-cyclohex-1-en-1-yl]-but-3-yne are dissolved in 50 ml of absolute tetrahydrofuran. The solution is added dropwise to a suspension of 2.4 g of lithium aluminium hydride in 180 ml of tetrahydrofuran while stirring at room temperature and the mixture obtained is heated under reflux conditions for 12 hours. The mixture is cooled, treated successively with aqueous ether and an aqueous ammonium chloride solution, then saturated with common salt and thoroughly extracted with ether. The ether extract is washed to neutrality, dried and evaporated. The resulting oily 4-[[4R]-4-hydroxy-2,2,6-trimethylcyclohex-1-en-1-yl]-but-3-en-2-ol [[3R]-3-hydroxy-β-ionol] is purified by adsorption on silica gel using hexane/ether (1:1) as the eluant.

2.1 g of [3R]-3-hydroxy-β-ionol are dissolved in 50 ml of absolute methanol. After the addition of 3.43 g of triphenylphosphine hydrobromide, the solution is stirred at room temperature for 12 hours. The solvent is subsequently evaporated under reduced pressure. The residue is dissolved in 80% aqueous isopropanol and shaken out twice with hexane. The isopropanol phase is evaporated under reduced pressure. The residue is dissolved in methylene chloride, dried over sodium sulphate and evaporated under reduced pressure to give 4-[[4R]-4-hydroxy-2,2,6-trimethylcyclohex-1-en-1-yl]-3-ene-2-triphenylphosphonium bromide.

1.605 g of 4-[[4R]-4-hydroxy-2,2,6-trimethylcyclohex-1-en-1-yl]-but-3-ene-2-triphenylphosphonium bromide are dissolved in 10 ml of isopropanol and

introduced at room temperature into a solution of 214 mg of 4,9-dimethyl-dodeca-2,4,8,10-tetraen-6-yne-1,12-dial [C_{14} aldehyde] in 10 ml of methylene chloride while stirring. The resulting homogeneous solution is treated with 0.336 ml of a 50% aqueous potassium hydroxide solution. The initially weakly yellow solution turns dark red after 2 to 3 minutes. The solution is stirred for a further 90 minutes at room temperature, then thoroughly extracted with methylene chloride. The combined methylene chloride extracts are washed to neutrality with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained crude *cis/trans*-[3R,3'R]-15,15'-didehydro-zeaxanthin which is brought to crystallisation by trituration with 3 ml of methanol in the cold, filtered off, dried and then subjected to the following isomerisation:

468 mg of *cis/trans*-[3R,3'R]-15,15'-didehydro-zeaxanthin are dissolved in 18 ml of acetonitrile. The solution is treated with 936 mg of a palladium oxide/barium sulphate catalyst containing 0.5% palladium, stirred for 12 hours at 70°C and subsequently cooled to room temperature. The catalyst is separated and repeatedly washed with a total of 60 ml of methylene chloride. The washings are combined with the filtrate and evaporated under reduced pressure. There is obtained crystalline all-*trans*-[3R,3'R]-15,15'-didehydro-zeaxanthin which melts at 208°—210°C after recrystallisation from methylene chloride and hexane.

Example 2.

20 g of [3R]-3-hydroxy- β -ionol and 30 g of 2,3-dichloro-5,6-dicyano-benzoquinone are dissolved in 400 ml of absolute dioxane. The solvent is heated for 1.5 hours at 50°—55°C. The solution is subsequently cooled to 0°C and the precipitated 2,3-dichloro-5,6-cyano-benzohydroquinone is filtered off. The filtrate is evaporated at 50°C under reduced pressure. The residue is dissolved in 250 ml of ether and extracted with a solution of 50 g of sodium dithionite in 250 ml of water. The ethereal phase is subsequently washed neutral with saturated aqueous sodium chloride solution, 1-N aqueous solution hydroxide solution and again with saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated to dryness. The residual [3R]-3-hydroxy- β -ionone can be purified by adsorption on silica gel (elution with ether) and is further reacted as follows:

To a solution of sodium acetylide in liquid ammonia (prepared from 60 ml of liquid ammonia, 2.68 g of sodium and acetylene in the usual manner) there are first added 6.0 ml of absolute ether and then, dropwise with stirring, a solution of 6.65 g of [3R]-3-hydroxy- β -ionone in 12 ml of ether. The mixture is transferred into a previously cooled autoclave and shaken for 16 hours at room temperature. The autoclave is subsequently cooled to -50°C, opened and freed from liquid ammonia with the simultaneous dropwise addition of n-hexane by evaporation. Thereafter, 100 g of ice and 20 g of glacial acetic acid are added to the mixture, and the n-hexane phase is washed with water, 5-N aqueous sodium hydrogen carbonate solution and again with water, dried over sodium sulphate and evaporated under reduced pressure. The residual [3R]-3-hydroxy-ethynyl- β -ionol is reacted further as follows:

12 g of [3R]-3-hydroxy-ethynyl- β -ionol are dissolved in 30 ml of n-hexane. The solution is hydrogenated while stirring at 20°C after the addition of 300 mg of Lindlar catalyst, 180 mg of 2-dimethylaminoethanol and 3 mg of 1,2-bis(2-hydroxyethylthio)ethane. After the termination of the hydrogenation, the catalyst is filtered off and the solvent is evaporated under reduced pressure. The residual [3R]-3-hydroxy-vinyl- β -ionol can be purified by adsorption on aluminium oxide (activity grade III; eluant: ether).

The [3R]-3-hydroxy-vinyl- β -ionol can also be prepared as follows:

A solution of 22.7 g of [3R]-3-hydroxy- β -ionone in 150 ml of absolute toluene is added dropwise to a solution of 28.4 g of vinyl-magnesium chloride in 114 ml of absolute tetrahydrofuran and 200 ml of absolute toluene. The mixture is subsequently stirred for 1 hour at room temperature, then cooled to 0°—5°C, treated with 0.6-N aqueous ammonium hydroxide solution and saturated aqueous ammonium chloride solution and extracted with ether. The ether extract is washed neutral with saturated aqueous sodium chloride solution, dried and evaporated to dryness. The residual oily [3R]-3-hydroxyvinyl- β -ionol can be purified by adsorption on aluminium oxide (activity grade IV; eluant: ether) and is reacted further as follows:

15.4 g of [3R]-3-hydroxy-vinyl- β -ionol are dissolved in 300 ml of absolute methanol. After the addition of 17.1 g of triphenyl phosphine, 26 mg of 2,6-di(*t*-butyl)-*p*-cresol and 8.5 ml of 25% aqueous hydrochloric acid, the solution is stirred

for 18 hours at room temperature. The solvent is subsequently evaporated off under reduced pressure at 40°C and the residue is crystallised from hot acetone. The precipitated [3R]-3-hydroxy- β -ionylidene-ethyl-triphenylphosphonium chloride melts at 211°—212°C after recrystallisation from methylene chloride/acetone/ethyl acetate; $[\alpha]_D^{25} = 57.2^\circ$ ($c = 1$ in chloroform).

1.291 g of [3R]-3-hydroxy- β -ionylidene-ethyl-triphenylphosphonium chloride and 162 mg of 2,7-dimethyl-octa-2,6-dien-4-yn-1,8-dial (C_{10} -dialdehyde) are dissolved in 20 ml of methylene chloride. To the resulting homogeneous solution is added 0.364 ml of a 38% aqueous potassium hydroxide solution at -10°C to -14°C with stirring. The mixture is stirred for 1 hour at -10°C to -14° and subsequently diluted with methylene chloride. The methylene chloride phase is washed neutral with water, dried over sodium sulphate and evaporated under reduced pressure. The residual crude cis/trans-[3R,3'R]-15,15'-didehydro-zeaxanthin is crystallised by trituration with 6 ml of warm 90% aqueous methanol. The crystal suspension obtained is cooled to -18°C, the [3R,3'R]-15,15'-didehydro-zeaxanthin filtered off, dried and subsequently isomerised as follows:

477 mg of cis/trans-[3R,3'R]-15,15'-didehydro-zeaxanthin are dispersed in 5 ml of n-heptane, treated with 5 drops of a 0.1% solution of iodine in chloroform and heated for 18 hours at 90°C while stirring. Subsequently, the n-heptane is evaporated off under reduced pressure. The residual all-trans [3R,3'R]-15,15'-didehydro-zeaxanthin melts at 210°—212°C after recrystallisation from methylene chloride/n-hexane.

The [3R]-3-hydroxy- β -ionylidene-ethyl-triphenylphosphonium chloride used in this Example can be replaced by [3R]-3-hydroxy- β -ionylidene-ethyl-triphenylphosphonium bromide which can be prepared as follows:

1.6 g of [3R]-3-hydroxy-vinyl- β -ionol are dissolved in 30 ml of absolute methanol. After the addition of 2.33 g of triphenylphosphine hydrobromide, the solution is stirred for 18 hours at room temperature. The solvent is subsequently evaporated off under reduced pressure and the residue crystallised from hot acetone. The [3R]-3-hydroxy- β -ionylidene-ethyl-triphenyl-phosphonium bromide obtained melts at 186°—187°C after recrystallisation from acetone; $[\alpha]_D^{25} = -55.1^\circ$ ($c = 1$ in chloroform).

The following Example illustrates the conversion of all-trans-[3R,3'R]-15,15'-didehydro-zeaxanthin, prepared according to Example 1 or Example 2, into all-trans-[3R,3'R]-zeaxanthin.

Example 3.

426 mg of palladium/calcium carbonate partially inactivated catalyst are suspended in 34 ml of absolute toluene and, after the addition of 46 ml of absolute ethyl acetate and 0.0125 ml of quinoline, pre-hydrogenated. After termination of the hydrogen uptake, the catalyst mixture is treated with 213 mg of all-trans-[3R,3'R]-15,15'-didehydro-zeaxanthin and hydrogenated further at atmospheric pressure and room temperature until uptake of 8.43 ml of hydrogen. The catalyst is filtered off and washed with ethyl acetate. The washings are combined with the filtrate, washed 3 times with 2 ml of 0.1-N sulphuric acid each time and then with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained partly oily [3R,3'R]-15-cis-zeaxanthin which is suspended in 15 ml of heptane and isomerised at 100°—110°C for 3.5 hours. All-trans-[3R,3'R]-zeaxanthin is precipitated crystalline in the cold; melting point 208.5—209.5° after recrystallisation from methylene chloride/methanol.

WHAT WE CLAIM IS:—

[3R,3'R]-15,15'-Didehydro-zeaxanthin of formula I hereinbefore.

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